REMARKS

Claims 1, 4-8, and 107-108 are currently under examination in the application. Claims 3, 11, 14-20, 23, 49-58, 60-64, 94-106, have been canceled. Claims 2, 9-10, 12-13, 21-22, 24-48, 59, and 65-93 have been withdrawn from consideration due to the Examiner's previous restriction requirement. Proposed amendments are submitted for claims 1, 4, 5, 107 and 108. Support for the proposed amendments is found throughout the specification, e.g., Abstract, ¶ [0007], [0010], [0016], [0028], [0030], [0031], and [0050]. These claims have been amended, withdrawn, or cancelled without prejudice to, or disclaimer of, the subject matter thereof. Applicants reserve the right to file divisional and continuing applications directed to the subject matter of any claim withdrawn, cancelled, or amended for any reason.

By these remarks and proposed amendments, Applicants do not acquiesce to the propriety of any of the Examiner's prior rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

I. Claim Objections

A. Claim 4

The Examiner has objected to claim 4 because it "should recite 'step (a)' instead of 'step (b).'" OA at 2. In response, Applicants have made the appropriate correction and accordingly request that this objection be withdrawn.

B. Claims 100-104

The Examiner has objected to claims 100-104 because they are identical to claims 4-8. OA at 2. Applicants have cancelled claims 100-104. Accordingly, Applicants request that this rejection be withdrawn.

II. Claim Rejections – 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 5 and 101 as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." OA at 3. More particularly, the Examiner asserts that "dependent claims 5 and 101 recite the limitation 'wherein said phosphodiesterase 4 inhibitor is administered before and during each training session,' which is a broader recitation

than the limitation in claim 1 which recites 'administering a phosphodiesterase inhibitor to said animal during rehabilitation.'" Id.

Claim 101 has been cancelled, and the proposed amendment to claim 5 now includes the limitation that the phosphodiesterase 4 inhibitor is "administered to said animal during said rehabilitation from stroke." Accordingly, Applicants request that the Examiner reconsider and withdraw this rejection under § 112, second paragraph.

III. Claim Rejections – 35 U.S.C. § 103

The Examiner has maintained the rejection of claims 1, 4-8, 100-104,[1] and 107-108 under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,547,979 ("Christensen") in view of the Merck Manual ("Merck"). OA at 4. This rejection is respectfully traversed.

In proceedings before the USPTO, "the Examiner bears the burden of establishing a *prima facie* case of obviousness based on the prior art."[2] Doing so requires the Examiner to meet at least four conditions: First, the Examiner must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Examiner must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all elements in the claim.[3] Fourth, if an obviousness rejection is based on a combination of prior art references, the Examiner must show a suggestion, teaching, or motivation ("TSM test') to combine the prior art references.[4]

Following the Supreme Court's decision in *KSR v. Teleflex*,[5] the TSM test must be applied flexibly to accord with the Court's approach of *Graham v. Deere.*[6] Such "a flexible TSM test remains the primary guarantor against a non-statutory hindsight

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[1] Claims 100-104 were cancelled per Section I.B and not considered further.

[2] *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003).

[3] *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

[4] *In re Dembiczak,* 175 F.3d 994, 998 (Fed. Cir. 1999).

[5] *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007).

[6] *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966).

analysis"[7] in obviousness cases, capturing the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art."[8]

Applicants hereby incorporate their previous responses and make the following additional points:

A. The Prior Art Does Not Teach or Suggest Administering a PDE4 Inhibitor in Conjunction with Cognitive Training.

To read on the pending claims, the prior art must include a teaching or suggestion to administer a PDE4 inhibitor *in conjunction with* cognitive training to enhance CREB pathway function *during* training. This it fails to do.

The operative term in the present claims is "conjunction." Conjunction is more than merely combining PDE4 inhibitor administration and cognitive training. Conjunction requires combining the two treatments so that CREB pathway function is enhanced in the appropriate neurons *during* training. As the specification discloses, "enhance CREB pathway function" means "the ability to enhance or improve CREB-dependent gene expression."[9]

Achieving this effect therefore requires that "[t]he dosage of augmenting agent administered to an animal is that amount required to effect a change in CREB-dependent gene expression, particularly in neurons."[10] The requirement in the pending claims that "the inhibitor is administered in conjunction with said cognitive training" is therefore a crucial limitation, which the Applicants respectfully assert is not taught or suggested by the prior art.

With this in mind, the Applicants turn to the Examiner's cited rationale for obviousness:

> Christensen clearly teaches, in general, the treatment of a stroke patient by administering a PDE4 inhibitor, which encompasses the entire treatment regiment including rehabilitation. . . .Nonetheless, it is clear that the Merck Manual teaches cognitive training after the acute phase of stroke. It is Examiner's position that it would be obvious to administer PDE4 inhibitors as taught by Christensen in combination with rehabilitation after the acute phase of stroke.

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[7] *Ortho-McNeil Pharma. v. Mylan Labs.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

[8] *KSR* at 418.

[9] See ¶ [0030] of the published application.

[10] See ¶ [0075] of the published application.

> Therefore, since both references teach treating stroke patients, it is obvious to combine there treatment regimens because both are drawn to the same purpose as well as for the combined therapeutic effect. For these reasons, Examiner submits that there would be reasonable expectation of success in treating stroke patients as instantly claimed.

OA at 9.

Based on this explanation, the Examiner's obviousness case appears to rely on at least two incorrect premises: first, that Christensen teaches administering a PDE4 inhibitor to treat stroke during rehabilitation; and second, that the combined teachings of Christensen and Merck would prompt one skilled in the art to administer the PDE4 inhibitor in conjunction with cognitive training such that CREB pathway function is enhanced during training. Applicants respectfully assert that each of these premises is flawed for at least the following reasons:

1. Christensen, in View of the Cited References and Prior Art as Whole, Does Not and Can Not Teach the Skilled Artisan to Administer PDE4 Inhibitors after the Acute Phase of Stroke.

The Examiner relies on Christensen as a primary reference to support a *prima facie* case of obviousness. According to the Examiner, "Christensen clearly does not limit administration of PDE4 inhibitors to any particular time period or treatment window of a stroke patient." OA at 7. Indeed, the Examiner asserts, "Christensen clearly teaches, in general, the treatment of a stroke patient by administering a PDE4 inhibitor, which *encompasses the entire treatment regimen including rehabilitation.*" OA 9 (emphasis added).

It appears that the Examiner's assertion is based entirely on claim 1, which is reproduced again here:

> A method of treating tissue injury, reperfusion injury, myocardial infarction, **stroke** or circulatory shock in a mammal, which comprises administering to said animal in need thereof an effective TNF inhibiting amount of a compound according to the formula . . .

Christensen, Col. 12, lines 27-54 (emphasis added).

It is respectfully submitted that the plain and direct interpretation of claim 1 is that it teaches one skilled in the art to use a TNF inhibitor to treat **stroke** (a stroke episode) **in a mammal**. The Examiner, however, continues to assert that claim 1 teaches using a TNF inhibitor to treat a **stroke patient** throughout the entire course of therapy, a time-

frame that encompasses all medical interventions and all subsequent stages of rehabilitation.

The Applicants respectfully continue to disagree with the Examiner's interpretation, which lacks "articulated reasoning" and adequate "rational underpinnings" in the record.[11] Indeed, it is submitted that this interpretation not only contravenes the plain meaning of claim 1; it contravenes Christensen and the prior art as whole, including the combined teachings of Christensen and Merck.[12]

Applicants have previously submitted a wealth of prior art directed to the biology of TNF and its role in stroke.[13] This evidence shows that a skilled artisan would only consider administering a TNF inhibitor during a narrow therapeutic window after the onset of stroke.[14] Moreover, this evidence counsels *against* using such inhibitors beyond the acute phase, pointing to a *beneficial* role for TNF, and the inflammatory response in general, in protecting neurons and promoting plasticity during the post-stroke recovery stage.[15]

Such a narrow therapeutic window, limited to the stroke episode, is also supported by Christensen as a whole, as well as the combination of Christensen and Merck. It is respectfully submitted that the Examiner has not properly considered Christensen,[16] failing to consider the other disclosures regarding stroke and TNF, found in the Detailed Description of the Invention:

> TNF also has pro-inflammatory activities which together with its **early** production (during the **initial** stage of an inflammatory event) make it a likely **mediator of tissue injury in** several important disorders including but not limited to, myocardial infarction, **stroke** and circulatory shock.

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[11] See *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.")

[12] *See In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995) ("In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.")

[13] August 8, 2009 Supplemental Reply, pp. 15-19.

[14] *Id*, pp. 15-18.

[15] *Id*, pp. 18-19.

[16] "It is impermissible within the framework of section 103 to pick and chose from any reference only so much of it as will support a give position to the exclusion of other parts necessary to the full appreciation of what a reference fairly suggests to one skilled in the art."

Christensen, Col. 5, lines 20-25 (emphasis added).

This disclosure corroborates the plain meaning of claim 1, as well as the evidence previously submitted by the Applicants, teaching an early and narrow therapeutic window for TNF inhibitors during the initial stage of an inflammatory event triggered by stroke. This view is further supported by Merck, which teaches –under the section entitled "Immediate Care" – that "[t]o be effective, treatments to minimize brain damage from acute stroke have to begin very soon after stroke onset."[17]

Applicants respectfully submit that the Examiner has not properly considered this rebuttal evidence. The evidence confirms that the only reasonable interpretation of the term "stroke" in claim 1 is its plain and direct meaning: the sudden death of brain cells resulting from a block (ischemia) or rupture (hemorrhage) of blood flow in the brain. This interpretation is fully corroborated by the disclosed role of a TNF inhibitor in Christensen. Christensen teaches that the inhibitor works by blocking the TNF-mediated inflammatory cascade triggered by *stroke*, thereby preventing or reducing its potential damage to the brain.

Accordingly, there can be no alternative interpretation but that Christensen only teaches or suggests TNF inhibitor administration ***during the acute phase*** of stroke, where it has the potential to help minimize brain damage. Applicants note further that this meaning of the term "stroke" also restores uniformity to claim 1, placing "stroke" in the same category as the other four conditions cited therein: They are all acute conditions triggered or exacerbated by TNF.

For all these reasons Applicants respectfully submit that the Examiner has not properly considered this rebuttal evidence. Applicants respectfully maintain that Christensen does not (and can not) teach or suggest administering PDE4 inhibitors outside the acute phase of stroke. That is, Christensen ***only*** bears on administering PDE4 inhibitors during the acute phase of stroke. Accordingly, one skilled in the art, in view of Christensen, would not consider administering a PDE4 inhibitor in conjunction with cognitive training during the rehabilitation phase of stroke, as required by the claims.

[17] Merck at 1455.

2. The Examiner's Responses to Applicant's Rebuttal Evidence Are Insufficient.

According to the Examiner, "Applicant's assertion that Christensen is simply teaching the administration of rolipram during the acute phase of stroke to reduce TNF **still** meet the limitations of the instant claims as it relates to the Merck Manual Reference." OA at 10 (emphasis added). At the outset, Applicants note that this argument should no longer be applicable because the pending claims clearly limit administration of PDE4 inhibitors and cognitive training to the rehabilitation phase.

Regardless, Applicants submit that this argument is incorrect, because it is based on the faulty and unsupported view that Merck teaches or suggests that the acute phase of stroke overlaps with cognitive training protocols during rehabilitation. In particular, the Examiner continues to assert the following:

> Furthermore, the Merck Manual clearly states that a training protocol should be started early as possible towards a patient's rehabilitation towards stroke. Such rehabilitation includes encouragement, orientation towards the outside environment, eating, dressing, toilet functions, other basic needs, passive exercise, particularly of paralyzed limbs, and breathing exercises." This time period may encompass when the patient is still in or just recovering from the acute phases of the stroke episode and beyond.

Applicants note again that the Merck Manual divides stroke care into two temporal phases: "Immediate Care" and "Rehabilitation and Aftercare." More particularly, "Immediate Care" does not mention or suggest training protocols, much less cognitive training protocols. Instead, Immediate Care refers to only "**passive** exercise, particularly of paralyzed limbs, and breathing exercises."[18] Applicants have previously pointed out that cognitive training protocols are active procedures that induce activity in specific brain regions involved in cognitive function.[19] To the extent that other manipulations listed by the Examiner may be applicable, they are discussed only in connection with "Rehabilitation and aftercare" and are therefore temporally distinct from "Immediate Care" procedures during the acute phase of stroke.

More generally, neither Merck nor Christensen provides any teaching or suggestion of the instantly claimed limitations that: (i) a PDE4 inhibitor "is

[18] Merck at 1455 (emphasis added).

[19] See, e.g., August 8, 2009 Supplemental Reply, pp. 19-23.

administered in conjunction with said cognitive training and enhances CREB pathway function during said cognitive training"; and (2) "***repeating*** said providing and said administering [ ]steps . . . one or more times." This issue is discussed in more detail in the next section.

B. There is No Motivation to Combine the Treatment Regimens of the Prior Art in the Same Way as in the Claimed Methods.

According to the Examiner "since both references teach treating stroke patients, it is obvious to combine these treatment regimens because both are drawn to the same purpose as well as for the combined therapeutic effect." OA at 9. This argument is respectfully traversed.

1. There is No Motivation for the Skilled Artisan to Administer PDE4 Inhibitors at the Same Time as Cognitive Training.

While one skilled in the art *might* be motivated to *serially* administer PDE4 inhibitors and cognitive training *at different times* to a stroke patient, *i.e.,* PDE4 inhibitors during the acute stage and cognitive training during the rehabilitation stage of stroke, respectively, there is *no* basis for combing the two treatment regimens simultaneously or in conjunction with each other.

As Applicants have previously discussed, the course of treatment for a stroke patient is divided into at least two temporally distinct stages: acute stroke and rehabilitation. Merck uses similar terminology, referring to (1) Immediate Care; and (2) Rehabilitation and Aftercare.

PDE4 inhibitors are administered to medically *unstable* patients *during* the acute stage to treat disease states mediated or exacerbated by TNF production. In particular, they serve to treat the damaging inflammatory response triggered by the initial stroke event. Beyond the acute stage, however, the prior art does not teach or suggest *any* role for such administration; indeed, as discussed above, such inhibitors would be contraindicated during the rehabilitation period. It is respectfully submitted that the Examiner has not pointed to any specific medical or scientific rationale to refute this view.

Cognitive training, on the other hand, is provided to medically *stable* patients *after* the acute stage to treat cognitive deficits. As previously discussed, such patients have typically undergone extensive screening and have been admitted into a

rehabilitation program.[20] Indeed, previously submitted evidence (discussed below) shows that such cognitive training protocols are not implemented until weeks, and more typically months, after the stroke episode.

That these two treatments may both serve the ultimate goal of treating stroke – as the Examiner observes – is therefore a red herring: This observation is a generalization that does not remove the distinct temporal and clinical properties that characterize these treatments. As already noted, if anything, the skilled artisan would implement these treatments serially in treating a stroke patient: administering PDE4 inhibitors at the onset of stroke during the acute phase; and after some time interval providing cognitive training to patients during rehabilitation. The references of record teach or suggest nothing more.

Moreover, with respect to the time interval between the acute phase and cognitive training, Applicants point again to their analysis of stroke references incorporated in the specification, which they discussed in their Supplementary Reply filed August 7, 2009. These references disclose cognitive training protocols directed to a range of cognitive impairments resulting from stroke. In every case in which there was available data, there was a post-stroke interval of at least several weeks, with most studies reporting a post-stroke interval of several months. Moreover, in each of these studies, the cognitive training protocol was an active procedure, and entry into the rehabilitation program typically required extensive screening and assessment.

These studies confirm the temporal and clinical distinction between acute stroke treatments and rehabilitation procedures. Therefore, it is respectfully submitted that there is no basis for administering PDE4 inhibitors *in conjunction* with cognitive training, so that CREB pathway function is enhanced during cognitive training, much less that this conjunction would occur at least twice – as required by the claims.

2. The Examiner's Responses to Applicant's Rebuttal Evidence Are Insufficient.

The Examiner continues to make several arguments in an attempt to counter the Applicants' rebuttal evidence, but they are all unavailing and based on the Examiner's personal opinion – with no proper support in the prior art.[21] Specifically, the Examiner

[20] See August 8, 2009 Supplemental Reply, pp. 19-22..

[21] *In re Kahn*, 441 F.3d at 988 (Fed. Cir. 2006).

asserts that the "[o]ne of ordinary skill in the art would interpret the teachings of Christensen to administer the PDE4 inhibitor after the acute phase of stroke episode since a full clinical diagnosis must be made before any treatment regimen is to be implemented" and that "the skilled artisan would also recognize that rehabilitation should be started as soon as a full diagnosis is made." OA at 8.

Applicants do not understand this argument, partly because it suggests that Christensen discusses administration of a PDE4 inhibitor in the context of "a full clinical diagnosis." But Applicants are not aware of such a disclosure, and the Examiner has not made any specific citations that clarify or support this argument. Moreover, the Examiner has not provided an explanation why such a full diagnosis would necessarily result in administration of a PDE4 inhibitor in conjunction with cognitive training to enhance CREB pathway function during training.

The Examiner also reasserts that "it is not clear when exactly does inflammation subside during the treatment period of a stroke patient, since low levels of inflammation could last well into the rehabilitation period" and then reminds the Applicants that "the standard for obviousness is not absolute but a reasonable expectation of success." OA at 8.

But as Applicants previously explained,[22] a mere possibility that something *could* happen is not inevitability and fails to meet the requirements for inherency. An inherent disclosure must be the "natural result flowing from the teachings or disclosure of the prior art,"[23] and the result must necessarily occur and not just be *possible* – or even *probable*.[24] Invoking a particular set of circumstances that might lead to administering the TNF inhibitor during the rehabilitation period, as the Examiner has done here, is therefore inadequate.[25] And even if such circumstances did occur, the Examiner has again not explained why the skilled artisan would administer a PDE4 inhibitor in conjunction with cognitive training during rehabilitation, so as to read upon the pending claims.

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[22] See January 28, 2010 Reply to Non-Final Office Action, p. 16.

[23] *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001).

[24] *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) ("The mere fact that a certain thing may result from a given set of circumstances is not sufficient. . . the disclosure [must be] sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function")

[25] *See in re Rijckaert,* 9 F.3d 1531, 1534 (Fed. Cir. 1993) ("The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency").

Applicants further note that a "reasonable expectation of success" applies to the ultimate determination of obviousness – not to the threshold inquiry of what the prior art teaches in the first place. The Examiner *still* must show that the prior art teaches or suggests all elements of the claimed invention. And if the element is an alleged inherent characteristic, the Examiner *still* show that it is *necessarily* present in the prior art. The Examiner has not made – and cannot make – such a showing here.

More generally, Applicants respectfully assert that the Examiner's argument is based only on opinion, as there is no proper rationale for why TNF inhibitors would be useful to treat inflammation beyond the acute phase of stroke. Christensen and the prior art provide no specific basis for this view. And Applicants have previously submitted evidence indicating a role for TNF in inflammation is at an early point in the cascade and that once the inflammatory cascade has been set in motion, one skilled in the art would recognize that TNF will have no effect.[26] Thus, even if the art did provide a basis for administering PDE4 inhibitors with cognitive training during rehabilitation, there is **no** reasonable expectation of success – and no expectation that such administration would *augment* the efficiency of cognitive training.

Finally, even if administration of a PDE4 inhibitors would necessarily be followed shortly thereafter by a cognitive training protocols – and there is no evidence for this – such a disclosure would also be deficient. The prior art still fails to teach or suggest administering the two procedures in proper conjunction with each other and then repeating this step one or more times, as required by the claims.

For all the reasons set forth here, Applicants respectfully assert that claims 1, 4-8, and 107-108 are not obvious over Christensen in view of Merck. Accordingly, Applicants request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

C. Proposed Amendments

The Applicants respectfully propose the following amendment, to be added at the end of independent claims 1, 107, and 108:

> wherein the inhibitor is administered in step (b) for the purpose of augmenting cognitive training.

[26] See, e.g., August 8, 2009 Supplemental Reply, pp. 15-18.

This amendment requires that the PDE4 inhibitor is administered to a stroke patient *for the purpose of augmenting cognitive training.* This limitation expressly captures the insight disclosed in this Application – that the efficiency of cognitive training protocols underlying stroke rehabilitation can be made more efficient by administering a PDE4 inhibitor in conjunction with cognitive training.

Entry of this amendment is respectfully requested. It does not require an additional search. And it is supported throughout the specification, which focuses on this very attribute (see, for example the citations listed at the beginning of the Remarks section). This limitation also adds patentable weight, because the amended claims would exclude patients that have not received a PDE4 inhibitor for the purpose of augmenting cognitive training during rehabilitation. Such claims would therefore exclude the prophetic patients treated in Christensen, who are not being administered PDE4 inhibitors for the purpose of augmenting cognitive training. Accordingly, it is respectfully asserted that entry of this amendment will render Christensen moot and expedite prosecution of this case.

CONCLUSION

Applicants have properly and fully addressed each of the Examiner's grounds for rejection. Applicants submit that the present application is now in condition for allowance. If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited. If there are any additional fees due in connection with the filing of this amendment, please charge the fees to undersigned's Deposit Account No. 50-1067. If any extensions or fees are not accounted for, such extension is requested and the associated fee should be charged to our deposit account

Respectfully submitted,

/djpelto Reg. No. 33754/

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